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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,334	04/28/2006	Albert Charles Gyorkos	2007_0505	5151

7590 03/16/2009

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EXAMINER	
FIERRO, ALICIA	
ART UNIT	**PAPER NUMBER**
4121	

MAIL DATE	DELIVERY MODE
03/16/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,334	GYORKOS ET AL.	
	Examiner	Art Unit	
	ALICIA L. FIERRO	4121	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *4,5 and 13-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-8,17 and 18* is/are rejected.

7)☒ Claim(s) *9-12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *13 July 2006 and 19 November 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-18 are pending in the instant application, filed April 28, 2006.

Priority

2. The instant application is a national stage entry of PCT/US2004/35648, filed March 2, 2007. The application appears to claim priority to U.S. Provisional Application No. 60/778,259, filed March 2, 2006 and U.S. Provisional Application No. 60/895,662, which has a filing date of March 19, 2007.

3. The Examiner notes that Applicant's claim to priority has not been perfected. In order to do so, the first line of the Specification must be amended to reflect the continuity of the application or an Application Data sheet reflecting the continuity can be submitted.

4. If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 119(e), a specific reference to the prior-filed applications in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet.

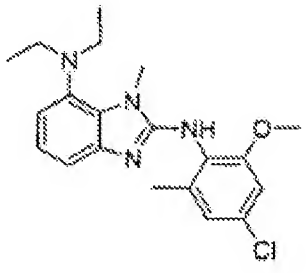
Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on July 13, 2006 was in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. Accordingly, the IDS document was considered and a signed copy of form 1449 has been enclosed herewith. The

information disclosure statement submitted on November 19, 2007 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed be submitted to the office. It has been placed in the application file, but the references which are crossed out in the signed copy of the 1449 form have not been considered. Additionally, documents marked with the notation "Abs only" have been considered only to the extent of their abstracts, as the remainder of the information was either not provided or not translated into English.

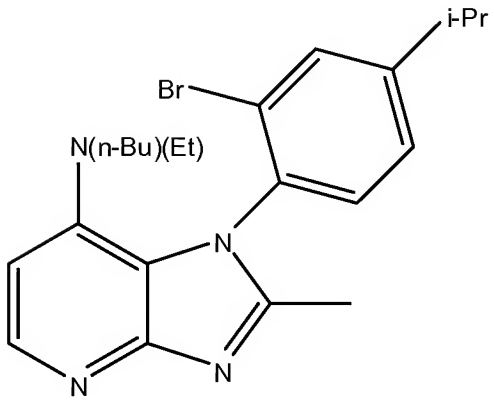
Election/Restrictions

6. Applicant's election of Group I (i.e. compounds of formula (I), a prodrug and agents comprised of said compounds, claims 1-12 and 17-18) in the reply filed on January 23, 2009 is acknowledged. Further, Applicant's election of the compound N^2-(4-chloro-2-methoxy-6-methylphenyl)-N^7,N^7-diethyl-1-methyl-1*H*-benzimidazole-2,7-diamine as well depression as the disease to be treated in the same reply is acknowledged. The elected species is a compound of Formula (I) wherein ring A is A'; X is C; X^1 is $NR^{5;}$ R^5 is hydrocarbyl (specifically methyl); W is a bond; R^1 is an amino substituted by two ethyl groups; Y^1=Y^2=Y^3=methyne; Z is NR^4; R^4 is H; and R^2 is an optionally substituted aryl, which is substituted by methoxy in the 2-position, chloro in the 4 position, and methyl in the 6 position. The elected compound has the following structure:



7. Claims 1-3, 6, 8-12 and 17-18 in Group I read on the elected species. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

8. Claims 4-5, 7, and 13-16 are withdrawn as being drawn to non-elected subject matter. MPEP § 803.02 provides guidelines for election of species in Markush-type claims. These guidelines were followed for the search and examination detailed herein. Applicant's elected compound was found to be free of the prior art, although the claims that read on the species are not allowable for the reasons discussed in the rejections below. Thus, the scope of the Markush claim has been extended to the next specie of a compound of formula I. The species that was examined has the structure shown below:



9. This is a compound of formula (I) wherein: ring A is A'; X is C; X^1 is $NR^{5;}$ R^5 is optionally substituted hydrocarbyl (specifically phenyl, substituted y 2-bromo and 4-isopropyl); W is a bond; R^1 is an amino substituted by and ethyl group and an n-butyl group; Y^1 is N; Y^2=Y^3=methyne; Z is a bond; and R^2 is an optionally substituted alkyl (specifically methyl). Claims 1-3, 7-8, and 17-18 read on the specie of the extended search. Because this species was not found to be free of the prior art, the search was not extended past this compound species. It was determined that the claims directed to depression as the disease to be treated and prevented are not allowable for the reasons discussed in the rejection below. Thus, the search was not extended to the next specie of disease. Therefore, the Markush-type claims were rejected and the subject matter drawn to nonelected species held withdrawn from further consideration. Claims 1-3, 6-12, and 17-18 were further examined, pursuant to MPEP § 803.02, to the extent necessary to determine patentability. It has been determined that the entire scope claimed is not patentable.

Objections

10. Claims 9-12 are objected to for being dependent upon a rejected base claim.

11. Claims 1-3, 6-12 and 17-18 are objected to for containing non-elected subject matter.

12. Claims 17-18 are objected to for being dependent upon claim 13, which is withdrawn from consideration. Appropriate correction is required.

13. Claims 17-18 are objected to for being drawn to a product (namely an agent) and being dependent upon a claim which is drawn to a **method** of using a different product (namely a compound of formula (Ia)). Appropriate correction is required.

Claim Rejections - 35 USC § 112

(First Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claim 2 is rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for prodrugs of the claimed compounds of formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. The nature of the invention
2. The state of the prior art
3. The predictability or lack thereof in the art
4. The amount of direction or guidance present
5. The presence or absence of working examples
6. The breadth of the claims
7. The quantity of experimentation needed, and
8. The level of skill in the art

The Nature of the Invention

The instant invention is drawn to prodrugs of a compound of Formula (I), namely the instantly elected compound N^2-(4-chloro-2-methoxy-6-methylphenyl)-N^7,N^7-diethyl-1-methyl-1*H*-benzimidazole-2,7-diamine, and the specie to which the search was extended (structure above in paragraph 7). Finding a prodrug is an empirical exercise. Predicting, for example, if a certain compound is in fact a prodrug that produces the active compound metabolically at a therapeutic concentration and a useful rate, is filled with experimental uncertainty. Attempts have been made to predict drug metabolism *de novo,* but this is still an experimental science. A prodrug of a compound must meet three tests. It must itself be biologically active. It must be metabolized to a second substance *in vivo* at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria requires a clinical trial setting and a large quantity of experimentation.

The State of the Prior Art

"Pro-drugs" are commonly known in the art as drugs which are administered in an inactive (or less active) form, and then metabolized in vivo into an active metabolite. As disclosed in Stella (Expert Opinions "Prodrugs as therapeutics"), "prodrugs are bioreversible derivatives of drug molecules used to overcome some barriers to the utility of the parent drug molecule. These barriers include, but are not limited to, solubility, permeability, stability, presystemic metabolism, and targeting limitations" (277). Stella, Valentino J, Expert Opinion of Therapeutic Patents, "Prodrugs as therapeutics," 2004 14(3): 277-280. Wolff et al. (Burger's

Medicinal Chemistry, 5th Ed., Vol. 1, pgs. 975-977, 1994) summarizes the state of the prodrug art, the lengthy research involved in successfully identifying a prodrug, and difficulties of extrapolating between species. With the limited direction and exemplification the specification offers, it is highly unpredictable whether or not the compounds of the Formula (1) will actually form effective prodrugs. Testa, Bernard, Biochemical Pharmacology, *Prodrug Research: futile or fertile?* 68 (2004) 2097-2106, discloses, on page 2098, the various challenges in prodrug research, concluding that all of these challenges may render prodrug optimization difficult to predict and achieve. Finally, Ettmayer, Peter, Medicinal Chemistry, *Lessons Learned from Marketed and Investigational Prodrugs,* 47(10) (2004) 2394-2404, discloses, on page 2401, that "the prodrug strategy should only be considered as a last resort to improve the oral bioavailability of important therapeutic agents" and "At the beginning of each prodrug program, there should be a clear definition of the problem to solve and defect to improve. The prodrug approach should not be misunderstood as a universal solution to all barriers to a drug's usefulness, and on page 2402, "The majority of all prodrug approaches face the challenge of identifying the optimal prodrug plus its activation system to enhance or prolong the concentration of the active principle at the site of action. Because of the complex situation of prodrug transport and processing, we recommend, especially for novel prodrug principles, that the first step should be to design and investigate different prodrug prototypes of high diversity (different attachment sites, linkers, promoieties, hydrolytic, oxidative, reductive activation, chemical vs. enzymatic activation)." Ettmayer et al. concludes that "the focus on victorious prodrugs should not be misunderstood as neglecting the inherent difficulties and additional layers of complexity a prodrug strategy might face." The evidence supports the conclusion that the

method of making claimed prodrugs is a subject for further study and experimentation.

The Level of Skill in the Art and the Predictability or lack thereof in the art

The level of skill of the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities as prodrugs. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any prodrug on its face, without evidence to support that particular prodrug. It is noted that the pharmaceutical art is unpredictable and requires the embodiments to be individually assessed for physiological activity. Thus, the more unpredictable the art, the more information in support of the invention is required to satisfy the statute. See *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Each embodiment of a prodrug must be supported by this invention in order to be enabled for the full range of prodrugs of compounds of the Formula (9).

The Amount of Direction or Guidance Present

The specification discloses in ¶ [0100] that a prodrug of Compound (I) or (Ia) is "(i) a compound that is converted into Compound (I) or (Ia) by an enzymatic oxidation, reduction, hydrolysis, or the like, and (ii) a compound that is converted into Compound (I) or (Ia) by hydrolysis with gastric acid or the like." Additionally, in the same paragraph the disclosure describes non-limiting examples of modifications to a hydroxyl group or a carboxyl group, but it is noted that neither of these functional groups are required to be in a compound of formula (I),

and even if the claimed compounds all contained either of the functional groups listed above, this portion of the specification provides no further insight into any particular prodrugs that would be converted to the instantly claimed compounds in vivo. However, as discussed above, it would be necessary for Applicant to provide evidentiary support for each embodiment due to the unpredictability in the art with regards to the success of prodrugs with some drugs over others. There are no working examples in the specification that show how to make or use prodrugs of the instantly claimed compounds. Additionally, the lack of examples in the specification is not sufficient to enable one skilled in the art to which it pertains to make and use any pharmaceutically acceptable prodrug as interpreted broadly by one of ordinary skill in the art. The specification does not adequately enable a method of making all prodrugs of the compounds that the claims encompass, as defined in the instant specification. The specification has limited exemplification thereof and of the necessary starting materials, as discussed *supra*.

As stated in Morton International Inc. v. Cardinal Chem, Co., 28 USPQ2d 1190:

> [T]he specification purports to each, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However... there is no evidence that such compounds exist... the examples of the patent do not produce the postulated compounds..., there is...no evidence that such compounds even exist.
>
> The same circumstance is true here.

The Breadth of the Claims

The claims are drawn to any compound which is converted to a therapeutically active compound of formula (1) after administration, and the term should be interpreted as broadly in the instant application as is generally understood in the art. As discussed above, this broad

disclosure cannot possibly enable one skilled in the art to which it pertains to make and use any pharmaceutically acceptable prodrug due to the unpredictability in the art with regards to the success of prodrugs with some drugs over others.

The specification provides limited support, as noted above, for the large number of prodrugs encompassed by the claims. The quantity of experimentation needed to make and use all of the prodrugs encompassed by the claims would be an undue burden on one skilled in the chemical art, since the skilled artisan is given inadequate guidance for the reasons state above. Even with the undue burden of experimentation, there is no guarantee that one would obtain the desired prodrugs in view of the Wolff reference.

The Quantity of Experimentation Needed

Based on the unpredictable nature of the invention and the state of the prior art and the breadth of the claims, one of ordinary skill in the pertinent art would be burdened with undue experimentation study to determine whether any pharmaceutically acceptable prodrug of compounds of the Formula (1) would successfully act as prodrugs as they are known in the art. Therefore, in view of the Wands factors discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which prodrugs, if any, would produce desired activity with compounds of the Formula (1) with no assurance of success. This rejection can be overcome by the cancellation of claim 2.

15. Claims 17-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for an agent to **prevent** any disease in which the CRF receptor is implicated **(**for example**,** depression) or to **treat** any disease in which the CRF receptor is implicated (for example, depression). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The Nature of the Invention

Claims 17-18 are drawn to an agent for treating or preventing any disease in which a CRF receptor is implicated, and specifically the instantly elected species of depression wherein the agent comprises any compound of formula (Ia).

The prophylactic treatment or "prevention" actually means to anticipate or counter in advance, to keep from happening, etc. and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds, compositions, and medicaments can be administered in order to have the "preventative" effect.

The State of the Prior Art and the Predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic preventative regimen on its face.

The instantly claimed invention is highly unpredictable as discussed below. It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would not readily recognize, in regards to their preventative effects on depression, whether or not the instantly claimed agents would have any effect.

With regards to the prevention of the onset of depression, for example, it has been established in the art that this disease is not preventable and therefore the claims to prevention are not enabled without further guidance (MayoClinic, <http://www.mayoclinic.com/health/depression/DS00175/DSECTION=causes>). The instant claims are drawn to preventing depression when a CRF receptor is implicated in the onset of the disease. However, without any prior knowledge of whether or not an individual will have abnormal CRF activity it is not possible to determine the at-risk population for which the claimed agent would be useful as a preventative agent, thus one would not be able to prevent **any** diseases stemming from abnormal CRF activity, including depression. Additionally, because there is no surefire way to predict whether an individual will necessarily develop depression in their lifetime, it is not possible to determine whether or not the claimed agents have any utility as preventative agents.

With regards to the treatment of any disease in which a CRF receptor is implicated, the art is established to be highly unpredictable. It is well known in the art that there are two classes of CRF receptor proteins; respectively, CRF_1 and CRF_2, each of which has a different subset of splice variants. While the splice variants within a given class of CRF receptors display no major

pharmacological difference, it has been established in the art that the binding profiles of the three CRF2 receptors ($CRF_{(2a)}$, $CRF_{(2b)}$, and $CRF_{(2c)}$) are strongly divergent from the binding profile of the CRF_1 receptor (International Union of Basic and Clinical Pharmacology [IUPHAR], <http://www.iuphar-db.org/GPCR/IntroductionDisplayForward?chapterID=1321>). This suggests a very high level of unpredictability in the art in terms of designing compounds that could potentially be effective for any CRF_1 or CRF_2 receptor.

The amount of direction or guidance present and the presence or absence of working examples

The specification discusses broadly the treatment of disorders related to the CRF receptor, explaining that a compound which can bind to a CRF receptor would be expected to be able to modulate the receptor and treat said disorders. However, it does not disclose how to make and use the instantly claimed compounds and agents for the treatment and prevention of depression, or any other disease in which a CRF receptor is implicated. The only guidance given to support the treatment of any disease is in vitro testing of the binding of 5 particular compounds with a CRF receptor. The example does not disclose whether the CRF receptor is a CRF_1 or CRF_2 receptor. As explained above, a compound that binds to one would not be expected to necessarily have a binding affinity for the other due to the divergent binding profiles. The specification also does not disclose any information specifically addressing which structural feature of the CRF receptors allow them to bind to the instantly claimed compounds, or how the interaction occurs. Thus, one of ordinary skill in the art would not be able to distinguish which compounds of instant formula (Ia) other than the five for which data is provided would be expected to have any significant binding affinity for the receptors. Additionally, the specification does not contain any evidentiary support or working examples to support the

prevention of the onset of depression or any other disorder in which a CRF receptor is implicated.

The breadth of the claims

The claims are extremely broad in that they encompass both the treatment and prevention of literally every disease implicating a CRF receptor using an agent comprised of any of the thousands of compounds which fall within the generic structure of (Ia).

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the inventions is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compound exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compounds of the instant claims for the treatment and prevention of these diseases, as a result necessitating one of skill to perform an exhaustive search for which compounds of the instant claims will be useful in order to practice the claimed invention, which specific CRF receptor the compound would bind, and finally which specific disease the agent could treat.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what compounds, out of all compounds, would be effective in preventing depression.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instantly claimed methods. In view of the breadth of the claims, the chemical nature of the invention, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which agents of the claimed compounds, if any, would treat depression or any other CRF receptor-related disorder with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

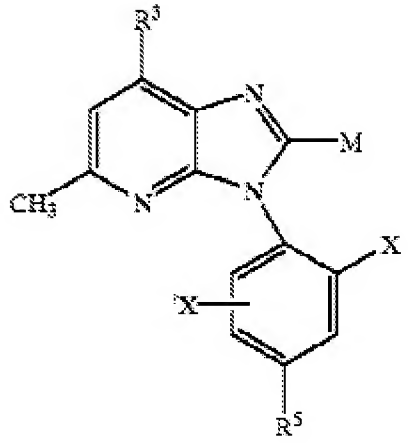
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

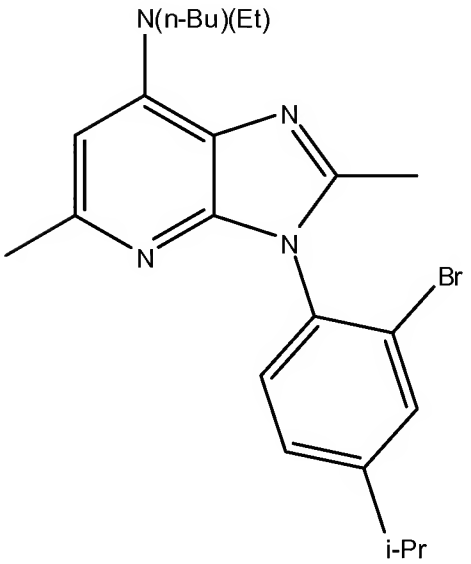
8. Claims 1, 3, and 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6107301 (published August 22, 2000).

9. The '301 patent discloses the following compound (Example 1000, synthetic Example 276) in Column 151, and also details its synthesis in Example 276, Column 125, lines 33-49:



Ex.	Synth. Ex	R^3	X	X'	R^5	M
1003*	276	—N(n-Bu)Et	Br	H	i-Pr	CH_3

The substitutions, as defined in the table, give the following compound:



Additionally, the ’301 patent discloses that the compounds synthesized are useful as inhibitors of the action of corticotrophin releasing factor (CRF) at its receptor protein in the brain

(column 5, lines 39-42). This compound is a *prima facie* obvious variant of the species of the extended search (listed in paragraph 7 above). The difference between the compound taught by the '301 patent and the instant claims is that the position of the substituted phenyl ring on the imidazole ring varies. The instantly examined species has the substituted phenyl ring attached to the other nitrogen of the imidazole ring. Thus, the compounds are positional isomers of one another.

With respect to positional isomers, MPEP 2144.09.II states, "Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. In re Wilder, 563 F.2d 457, 195USPQ 426 (CCPA 1977).

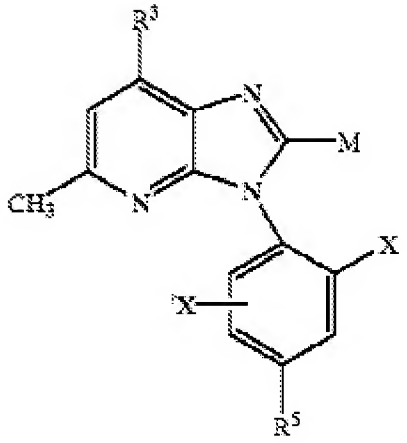
In positional isomerism, a functional group changes position on the chain or ring. The positional isomers of the instant claims and of the '301 patent are useful modulators of CRF activity. As stated in In re Norris 179 F.2d 970, 84 U.S.P.Q. 458 (C.C.P.A. 1970), a novel useful compound that is isomeric with the prior art compound is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compound. In other words, if the positional isomers of the instant application produced unexpected results that would not be obvious to one of ordinary skill in the art, they would be patentably distinct; however, there is no evidence of such results in the instant application.

Additionally, hydrogen and methyl are deemed to be obvious variants of each other. In re Wood, 199 USPQ 137. Thus, replacing the methyl on the benzimidazole ring with a hydrogen is an obvious variation of the known compound.

The motivation to make the instantly examined species derives from the expectation that structurally similar compounds would possess similar biological activity (i.e. they would be pharmacologically active and useful as CRF modulators). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make the instantly examined species by modifying a hydrogen on the benzimidazole ring to a methyl group and making a positional isomer of the compound taught by the '301 patent by changing the ring position of the instant "R^5" substituent.

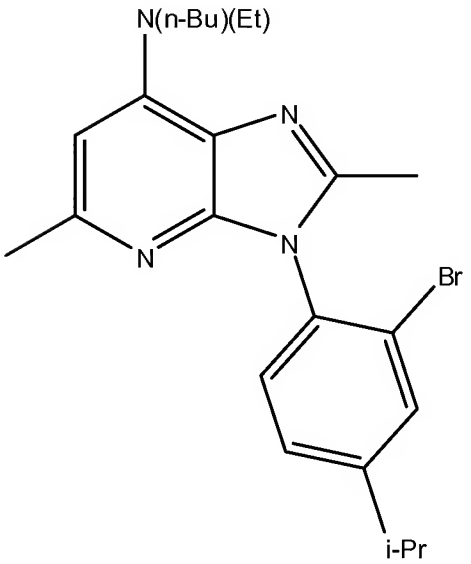
10. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6107301 (published August 22, 2000), in view of Patani et al., *Chem Rev.*, 1996, 96, 3147-76.

The '301 patent discloses the following compound (Example 1000, synthetic Example 276) in Column 151, and also details its synthesis in Example 276, Column 125, lines 33-49:



Ex.	Synth. Ex	R^3	X	X'	R^5	M
1003*	276	—N(n-Bu)Et	Br	H	i-Pr	CH_3

The substitutions, as defined in the table, give the following compound:



Additionally, the ’301 patent discloses that the compounds synthesized are useful as inhibitors of the action of corticotrophin releasing factor (CRF) at its receptor protein in the brain

(column 5, lines 39-42). This compound is a *prima facie* obvious variant of the species of the extended search as discussed in the rejection above. Additionally, this compound renders obvious the genus claimed in claim 6. The difference between the compound taught by the '301 patent and the instant claims is that the position of the substituted phenyl ring on the imidazole ring varies. The instantly examined species has the substituted phenyl ring attached to the other nitrogen of the imidazole ring. Thus, the compounds are positional isomers of one another. Additionally, the Y1 position of this compound is N rather than CR3a, as in claim 6, so the compounds are bioisosteres of one another.

With respect to positional isomers, MPEP 2144.09.II states, "Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. In re Wilder, 563 F.2d 457, 195USPQ 426 (CCPA 1977).

In positional isomerism, a functional group changes position on the chain or ring. The positional isomers of the instant claims and of the '301 patent are useful modulators of CRF activity. As stated in In re Norris 179 F.2d 970, 84 U.S.P.Q. 458 (C.C.P.A. 1970), a novel useful compound that is isomeric with the prior art compound is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compound. In other words, if the positional isomers of the instant application produced unexpected results that would not be obvious to one of ordinary skill in the art, they would be patentably distinct; however, there is no evidence of such results in the instant application.

Additionally, hydrogen and methyl are deemed to be obvious variants of each other. In re Wood, 199 USPQ 137. Thus, replacing the methyl on the benzimidazole ring with a hydrogen is an obvious variation of the known compound.

Finally, Patani et al. teaches that "bioisosterism represents one approach used by the medicinal chemist for the rational modification of lead compounds into safer and more clinically effective agents," and further that the concept of bioisosterism is "intuitive" (page 3147, Introduction, column 1-column 2). Bioisosteric substitutions are well-known in the art. For example, NH and CH_2 are taught to be ring equivalent bioisosteres by Patani et al (see page 3158, section E, especially Figure 31). Thus, claim 6 is made obvious insofar as R3a is hydrogen.

The motivation to make the instantly examined species derives from the expectation that structurally similar compounds such as positional isomers and bioisosterse would possess similar biological activity (i.e. they would be pharmacologically active and useful as CRF modulators). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make the instantly examined species by modifying a hydrogen on the benzimidazole ring to a methyl group, making a positional isomer of the compound taught by the '301 patent by changing the ring position of the instant "R^5" substituent, and creating a bioisosteric ring substitution of CH for N in the pyridine ring.

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALICIA L. FIERRO whose telephone number is (571)270-7683. The examiner can normally be reached on Monday - Thursday 6:00-4:30 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on (571)272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AF

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